

**REMARKS**

Claims 1 to 41 have been cancelled and new claims 42-80 have been added. No new matter is added by virtue of the within amendments; support therefore can be found throughout the specification and in the original claims of the application. For instance, the newly presented claims are largely based on original claims 32-38 and combinations thereof. Additionally, several amendments are directed to matters of form, e.g., removing multiple dependencies and otherwise conforming the claims to U.S. patent practice.

As an initial matter, the Office Action objects to the earlier filed Declaration in that certain manual alterations were not initialed and/or dated. The undersigned Attorney has initialed and dated such alterations on behalf of the inventors as their duly authorized representative. The alterations were not substantive in that they merely sought to update two instances of the inventors' residential information. In further support thereof, an updated Application Data Sheet is being filed concurrently herewith.

Claims 5-9, 13-21, 25-31, 35-38 and 42 are objected to under 37 CFR 1.75(c). The subject matter of the noted claims has been rewritten in the newly presented claim set. Improper multiple dependencies have been eliminated. Proper consideration and examination are therefore requested.

Claim 10, 24, 33 and 40 also are objected to on the basis of various informalities. The newly presented claims reflect correction of each of these informalities.

Withdrawal of each of the aforementioned objections is requested.

Claims 1-4 are rejected under 35 USC 112, second paragraph, as not reciting proper composition claim form. Likewise, claims 2-4, 11, 12, 22-24, 32-34 and 39-41 are rejected under 35 USC 112, second paragraph for recitation of the phrases "such as" and "preferably". Claim 12 is further rejected under 35 USC 112, second paragraph, for recitation of the term "spiked". It is respectfully submitted that the newly

presented claims omit the objectionable terminology and reflect correction of each of these informalities. Withdrawal of the rejections under 35 USC 112, second paragraph, is requested.

The prior art rejections are summarized as follow:

Claims 1-3, 10-12, 32, and 39-41 are rejected under 35 USC 102(b) over Wahlestedt et al. (WO 01/25248);

Claims 1-4, 10-12, 22, 23 and 39-41 are rejected under 35 USC 102(b) over Orum et al. (WO 01/48190); and

Claims 1-3, 10-12, 32-34 and 39-41 are rejected under 35 USC 103(a) over Wahlestedt et al. (WO 01/25248).

The rejections are respectfully traversed. The cited references do not teach or suggest the present invention in any manner sufficient to sustain the instant rejections. Nonetheless, it is noted that original claims 1-41 stand cancelled in favor of new claims 42-80. The claims of the application have been amended to further define and clarify the features of the invention.

New independent claim 42 recites:

An oligonucleotide which has the formula (in 5' to 3' order): A-B-C-D, in which  
A represents a sequence of locked nucleotide units;  
B represents a sequence of non-locked nucleotide units,  
C represents a sequence of locked nucleotide units; and  
D represents a non-locked nucleotide unit or a sequence of non-locked nucleotide units.

Wahlestedt et al. do not appear to disclose an oligonucleotide of formula A-B-C-D, i.e. a gapmer (A-B-C) with the inclusion of one or more non-locked nucleotides located in the 3'-end relative to C. Therefore, it is respectfully submitted that the subject matters of new claim 42 (as well as original claim 32 on which claim 42 is based) and of the claims which depend therefrom are neither taught nor suggested by Wahlestedt et al. Orum et al. are likewise deficient and cannot sustain the rejection.

In contrast to the art cited, the present inventors have found that the inclusion of one or more non-locked nucleotides located in the 3'-end relative to C provides a highly effective gapmer oligonucleotide for down-regulation of a target gene. This is clear from the specification of the current application, which discloses numerous oligonucleotides comprising a D region. For example, attention is directed to Figures 5A and 5B, which illustrate highly effective down-regulation of Ha-ras mRNA in 15PC3 cells when using oligonucleotides 2754, 2755, 2748, 2749 and 2742, all of which comprise a D region.

Therefore, it is respectfully submitted that the subject matters of independent claim 42 and of its dependent claims are novel and non-obvious over the cited art. In summary, the cited art fails to disclose or even motivate inclusion of a region D in a gapmer. Additionally, as noted above, it was observed by the present inventors surprisingly that gapmer oligonucleotides which comprise a region D were highly effective in down-regulation of a target gene.

In view of the above amendments and remarks, Applicant believes the pending application is in condition for allowance.

Dated: April 3, 2006

Respectfully submitted,

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Application No. 10/717,434  
Amendment dated April 3, 2006  
Reply to Office Action of November 3, 2005  
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Docket No.: 58404(71432)

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